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Original Research Article

Persistence and Prognostic Implications of Orthostatic Hypotension in Older Individuals with Mild-to-Moderate Dementia

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Key Words
Dementia · Orthostatic hypotension · Survival analysis

Abstract
Aim: To study the course and prognostic implications of orthostatic hypotension (OH) in older individuals with mild-to-moderate dementia. ***Methods:*** Referrals to outpatient clinics specialising in old age psychiatry and geriatric medicine in the counties of Rogaland and Hordaland in western Norway with a first-time diagnosis of mild dementia were consecutively asked for inclusion. A total of 211 participants underwent a comprehensive baseline assessment with annual follow-ups. Patients with OH at both baseline and the 1-year follow-up were classified as having persistent OH. Outcome measures were the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating sum of boxes (CDR-SB), and time to death. ***Results:*** From baseline to the 4-year follow-up, 30–45% of the participants had OH at each follow-up. In multivariable analysis, persistent OH was not significantly associated with either the longitudinal course of MMSE or CDR-SB scores or survival. ***Conclusions:*** OH was moderately prevalent over 4 years in older individuals with mild dementia, and persistent OH did not predict either cognitive or functional decline or survival.

Introduction

Orthostatic hypotension (OH) [1, 2], corresponding to the syndrome known as ‘classical OH’ [3], is commonly diagnosed in older individuals [4], including those with dementia [5–7]. Generally, as well as in a single older patient, OH may have several causes, including age-related changes in the cardiovascular and autonomic nervous systems [8], autonomic dysfunction (which is common in neurodegenerative dementias) [9], medication [10], and acute illness with a reduction in intravascular volume [8]. OH is associated with falls [11],

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coronary heart disease, and mortality [12]. It also has been associated cross-sectionally with cognitive impairment in the elderly [13, 14].

However, only few studies have explored the potential longitudinal implications of OH with regard to cognitive function in older individuals with mild dementia. Viramo et al. [15] found no longitudinal association between OH and cognition over a period of 2.5 years; cognitive decline was predicted only by old age and a low level of formal education. Likewise, not much is known with respect to the potential implications of OH for activities of daily living (ADL), although a previous cross-sectional study found that higher autonomic symptom scores and postural dizziness in non-Alzheimer's dementias were associated with poorer outcomes in ADL [16]. Concerning the potential impact of OH on survival in dementia, Stubendorff et al. [17] recently found that patients with dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) with persistent OH over a period of up to 6 months had a significantly shorter survival than those without persistent OH.

OH is potentially treatable [18, 19], meaning that its possibly negative impact on cognitive function and ADL might be alleviated. Notably, in the majority of dementia patients with OH, classical symptoms such as dizziness or unsteadiness seem to be absent [20].

The reproducibility of OH on repeated measurements has been studied in various populations [21–25], with inconsistent results [26]. It has not, to our knowledge, been established whether, and to what extent, OH is persistent over the longer term in older individuals with dementia. In a previous study, we reported the cross-sectional prevalence of OH in individuals with mild dementia [7]. Here, we wanted to study the longitudinal course of OH in the stages of mild-to-moderate dementia and to investigate the hypothesis that patients with persistent OH have a more rapid cognitive and functional decline as well as a shorter survival than those without OH.

Subjects and Methods

Ethics Statement

The study was approved by the Regional Committee for Medical and Health Research Ethics (REC West) and the Norwegian authorities for the collection of medical data. Each patient provided written consent to participate in the study after the procedures had been explained in detail to him/her and a caregiver, usually the spouse or an offspring.

Subjects

From March 2005 to April 2007, all referrals to the 5 outpatient clinics specialising in old age psychiatry and geriatric medicine in the counties of Rogaland (Stavanger and Haugesund) and Hordaland (Bergen) in western Norway were screened for patients with a first-time diagnosis of mild dementia (according to the DSM-IV [27]) having a Mini-Mental State Examination (MMSE) [28] score of 20 or more (upper limit: 30). Additionally, the 3 neurology outpatient clinics in the same area were contacted, and they agreed to refer new cases with mild dementia to one of the participating centres. The patients and caregivers were first seen by a study clinician, who performed a structured clinical interview. The comprehensive assessment procedure included a detailed history, using a semi-structured interview, a clinical evaluation (including physical, psychiatric, neurological, and neuropsychological examinations), and routine blood tests.

Procedures

The patients were followed up annually with the same assessment battery for the first 2 years, thereafter with a simplified test battery.

Dementia Diagnosis

Diagnoses were made after a detailed evaluation, as previously described [29], including the use of standardised clinical assessments of psychiatric symptoms, parkinsonism, and cognitive fluctuations as well as brain magnetic resonance imaging (MRI) [30] and blood tests. The diagnoses of Alzheimer's disease (AD), DLB, PDD, and vascular dementia (VaD) were made according to consensus criteria [31–34], and those of alcoholic dementia and frontotemporal dementia (FTD) according to the DSM-IV criteria and the Lund-Manchester criteria [35], respectively. Patients with acute delirium or terminal illness, those recently diagnosed with a major somatic disease, and those with previous bipolar or psychotic disorder were excluded from the study. In the present study, the patients having DLB and those having PDD were combined into one group (Lewy body dementia, LBD) because these conditions have several biological and clinical similarities [32, 36].

Clinical Assessment

The MMSE was used as a measure of cognitive function. The Clinical Dementia Rating sum of boxes [37] (CDR-SB) was employed as a composite measure of cognitive and general function [38, 39]. For the assessment of physical comorbidity, we employed the Cumulative Illness Rating Scale (CIRS). This scale measures the chronic medical illness burden while also taking into account the severity of a chronic disease. It was scored by an experienced geriatrician in accordance with the guidelines [40]. Depression was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) [41, 42].

MR images were rated visually for the severity of white matter hyperintensities (WMH), using the Scheltens scale [43], by an experienced rater blinded to the clinical data. For further details, see Soennesyn et al. [30]. In the present study, we used the Scheltens total WMH score only. For more details on the selection, diagnostic, and assessment procedures, see Aarsland et al. [29].

Survival and Mortality

We registered all deaths from study inclusion until October 1, 2012.

Blood Pressure Measurements and Definitions of OH

Blood pressures were measured using an analogue sphygmomanometer, once with the subject in the supine (n = 123) or sitting position (n = 83; n = 5 unknown whether supine or sitting) and then once within 3 min after standing up. If more than 1 standing measurement had been made for a given subject (n = 14 at the 1-year follow-up; n = 1 at the 2-year follow-up), the lowest systolic and diastolic blood pressure values were used for the diagnosis of OH [12].

OH was defined according to the consensus criteria [1, 2] as a reduction in systolic blood pressure of at least 20 mm Hg, or in diastolic blood pressure of at least 10 mm Hg, within 3 min of standing. 'OH+' ('persistent' OH) was defined as having OH both at baseline and at the 1-year follow-up, and 'OH–' ('never' OH) as not having OH at either of these examinations. The assessments took place during normal office hours (i.e. 8 a.m. to 4 p.m.).

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics version 20 and R version 2.15.2. The baseline characteristics are presented as quartiles (continuous variables) and proportions (dichotomous variables). The proportions of patients with OH at each assessment are presented with continuity-corrected 95% confidence intervals (95% CI; http://vassarstats.net/). The clinical outcome measure scores (MMSE and CDR-SB) in those with and those without OH at each assessment were compared using independent-samples t tests.

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Table 1. Baseline clinical characteristics of the patients with OH measurements at both baseline and the 1-year follow-up and of those not having these two measurements

	OH measurements both at baseline and 1-year follow-up		Missing data (n = 211)
	yes (n = 133)	no (n = 78)	
Age, years	77.2 (71.0–82.0)	76.5 (70.0–80.6)	0
Women, n (%)	79 (59)	45 (58)	0
Education, years	9 (8–12)	8 (7–10)	7
MMSE score	24.0 (22.0–26.0)	23.0 (21.8–25.3)	2
CDR-SB score	4.5 (3.5–6.4)	5.5 (3.5–8.0)	16
AD, n (%)	91 (68)	47 (60)	0
DLB/PDD, n (%)	28 (21)	26 (33)	0
VaD, n (%)	8 (6)	3 (4)	0
Other dementias (FTD, Alc.), n (%)	6 (5)	2 (3)	0
MADRS total score[a]	6 (3–13)	7 (4–11)	1
Using antidementia medications, n (%)[b]	52 (39)	26 (34)	2
Smoker (former/current), n (%)	61 (47)	34 (47)	8
CIRS score[c]	6 (4–7)	6 (4–8)	3
Cardiovascular disease, n (%)[d]	41 (33)	25 (35)	14

Values denote medians with IQR in parentheses unless specified otherwise. Alc. = Alcoholic dementia.
[a] Range: 0–60. [b] Acetylcholinesterase inhibitor or memantine. [c] Range: 0 (no impairment) to 52 (extremely severe impairment). [d] History of stroke or coronary heart disease.

The survival analysis was conducted with Kaplan-Meier plots and Cox proportional hazards modelling in SPSS. As explanatory variables, we used OH+ (yes/no) together with various combinations of potential confounders (see below). The presence of time-dependent effects of OH was tested by means of the TIME PROGRAM command.

Analyses of the longitudinal outcomes were performed with generalised estimating equations (GEE) in SPSS, in which OH+ (yes/no), time, and the interaction between OH+ and time were entered as model effects, along with various combinations of potential confounders from baseline measurements: centre, age, sex, education (in years), smoking [44] (ever/never), AD versus other dementia, dementia medication (acetylcholinesterase inhibitor or memantine – yes/no), CIRS score, cardiovascular disease (history of stroke or coronary heart disease – yes/no), MADRS score, and MMSE or CDR-SB score (the one that was not the dependent variable). Four modelling schemes were tried: (1) no adjustment, in which only terms involving OH+ and/or time were included; (2) adjusting for age and sex; (3) adjusting for all available potential confounders, and (4) adjusting for the variables that were deemed important after a (manual) stepwise reduction of the model based on likelihood ratio tests (though keeping OH+, time, the interaction OH+/time, sex, and age in the model). All the results were based on a robust estimation of unstructured correlation matrices.

As informative dropout due to death [45, 46] was suspected in this study, we also ran analyses which were intended to deal with this issue. The function 'joineR' in R [47] is based on a linear mixed model for the longitudinal outcome and a proportional hazards model for the survival outcome, which are linked through common random effects. The various models described above were fitted, allowing for various kinds of links between the random effects relating to the longitudinal outcome and the frailty relating to the survival outcome. The optimal structure of random effects for each combination of fixed effects was determined by

Table 2. Point prevalence and persistence of OH from the previous examination among the patients evaluated (baseline to 4-year follow-up)

	Baseline	1-year follow-up	2-year follow-up	3-year follow-up	4-year follow-up
Point prevalence of OH	74/169 (44; 36–52)	51/163 (31; 24–39)	36/121 (30; 22–39)	50/112 (45; 35–54)	39/87 (45; 34–56)
Persistence of OH	–	29/58 (50; 37–63)	15/34 (44; 28–62)	14/24 (58; 37–77)	14/28 (50; 31–69)

Values denote numbers with percentages and 95% CI in parentheses.

the Akaike information criterion [48]. Normal-based confidence intervals and Wald χ^2 p values for fixed and random effects were estimated by non-parametric (resampling) bootstrapping (200 bootstrap samples) [49]. Since the purpose of these joint models was to improve on the results for the longitudinal outcomes 'CDR-SB score' and 'MMSE score', we limited the covariates for the survival outcome to just OH+ (yes/no), age, and sex.

The treatment of missing data amounted to excluding from each analysis the subjects with missing observations of the relevant variables (available case analysis), assuming non-informative missingness. The exception to this was the joint analyses, where the effects of dropouts due to death were accounted for implicitly in the models.

Results

Of the 211 patients available at baseline, 133 had OH measurements at both baseline and the 1-year follow-up. Patients with these two OH measurements had a somewhat longer education and higher cognitive performance than those not having these two measurements (table 1). Otherwise, the groups did not differ substantially with respect to the relevant baseline characteristics.

Of the 133 patients, between 21 and 44 were recruited from each of the 4 largest participating centres, but only 4 patients were recruited from the smallest, fifth centre. There were 91 patients with AD and 28 having LBD. With respect to the variables in table 1, these groups differed significantly in terms of sex (69 vs. 43% women, $p = 0.021$), MADRS score (5 vs. 12, $p = 0.001$), use of antidementia medications (51 vs. 18%, $p = 0.004$), and CIRS total score (5.0 vs. 6.5, $p = 0.003$).

A total of 94 of the 211 patients included at baseline did not complete the 4-year follow-up. Of these, 67 died prior to the expected 4-year follow-up time. Of the remaining 27 patients, 8 withdrew from the study, 1 moved, 6 were excluded for various reasons, and 12 missed the follow-up for unknown reasons.

Course of OH

At each assessment, OH measurements were available for 75–86% of the participating patients. For the point prevalence and persistence of OH from the previous examination among those measured, see table 2. Among the 85 patients with OH measurements at baseline, the 1-year follow-up, and the 2-year follow-up, 32 'never' had OH, 18 had OH once, 27 twice, and only 8 had OH at all 3 measurements.

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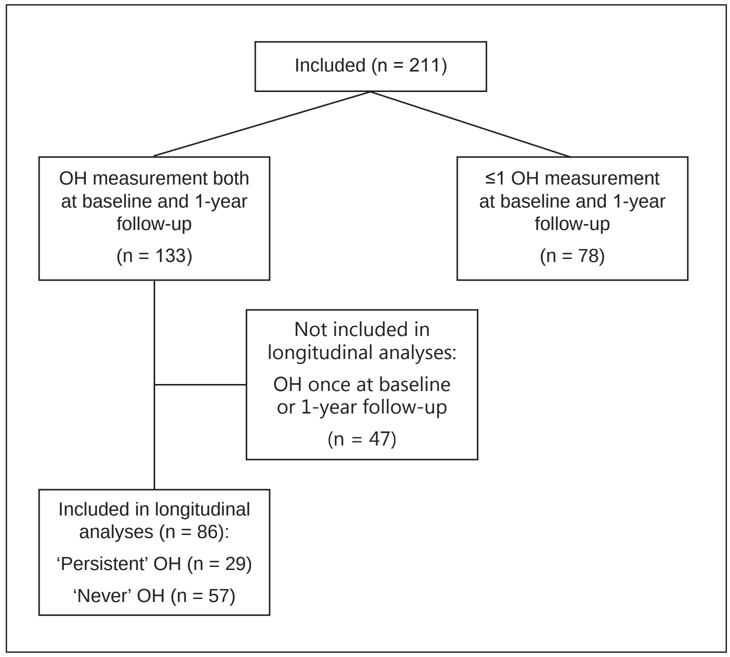

Fig. 1. OH classification flow chart.

Of the 133 patients who had complete data on OH measurements at both baseline and the 1-year follow-up, 29 were OH positive on both occasions and were thus classified as 'persistent OH' (OH+), whereas 57 were OH negative on both occasions and were classified as 'never OH' (OH–; fig. 1). There were no significant differences in mean non-standing systolic or diastolic blood pressure between those measured in the supine and those measured in the sitting position at baseline (data not shown). The general condition of the patients in these groups (OH+ and OH–) at baseline did not differ significantly [good general condition (compared with average or bad): 93 vs. 85%, p = 0.482], and the median CIRS total score was 6.0 (potential maximum score: 52) in both groups (p = 0.491). There were no significant differences between the OH+ and the OH– group with respect to history of hypertension (55 vs. 44%, p = 0.437), prevalence of diabetes mellitus type 1 or 2 (13 vs. 0%, p = 0.090), prevalence of kidney disease (median CIRS renal score 0 in both groups), use of at least 1 medication associated with OH (antianginals, antihypertensives, tricyclic antidepressants, paroxetine, MAO inhibitors, dopamine agonists, diazepam, dipyridamole, phenothiazines, clozapine, quetiapine, olanzapine, or haloperidol; 59 vs. 54%, p = 0.831), use of antihypertensive medication (55 vs. 46%, p = 0.592), or Scheltens total WMH score (median score: 11.5 vs. 14.0, p = 0.525). Baseline serum lipid values were available for only 3 of these patients.

OH and Survival

As of October 1, 2012, a total of 14 patients out of 29 (48%) had died in the OH+ group, whereas 29 out of 57 (51%) had died in the OH– group. A Kaplan-Meier plot with separate survival curves for each OH group is shown in figure 2. As can be seen, the curves are very similar. The mean survival time in the OH– group was 5.7 years (95% CI: 5.2–6.3), and in the OH+ group 5.8 years (95% CI: 5.1–6.5); the corresponding median survival times were 6.8 and 6.2 years. A Cox regression model showed no significant effect of OH status (unadjusted p = 0.999). Adjusted for age and sex (both contributing significantly to the model), the estimated HR for OH+ versus OH– was 0.83 (95% CI: 0.44–1.57, p = 0.562). Adding other baseline variables to the model (smoking, CDR-SB score, MMSE score, CIRS score, cardiovascular

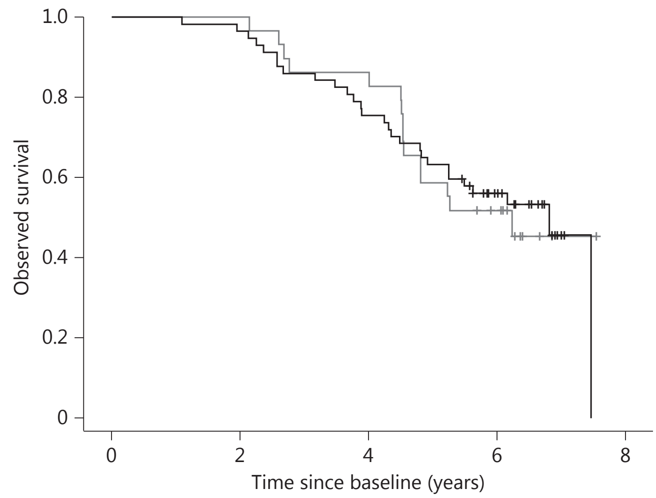

Fig. 2. Observed survival for the OH+ group (grey) and for the OH– group (black).

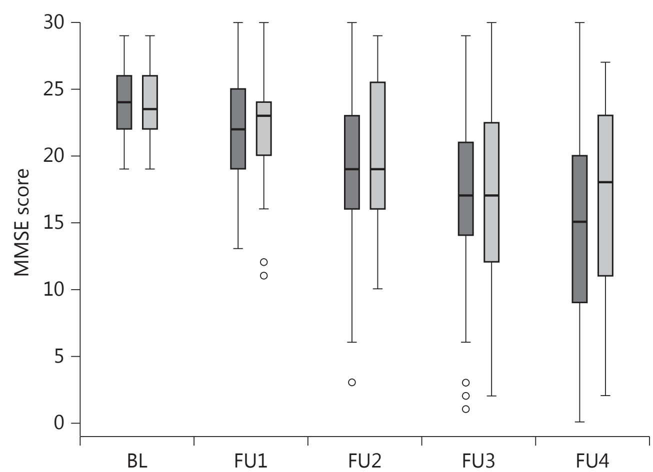

Fig. 3. Box plot of MMSE scores from baseline (BL) to 4-year follow-up (FU4). Light grey: patients with OH at each examination. Dark grey: patients without OH at each examination.

disease, AD vs. non-AD dementia, or centre) did not change the results substantially; neither did OH status interact statistically significantly with time in the tested models.

OH and Function

Cognitive and general function declined as expected, as was measured with the MMSE and the CDR-SB. At the 4-year follow-up, the median MMSE score was 15.0 (IQR: 10.0–22.8) and the median CDR-SB score 13.0 (IQR: 8.4–15.3) among those having two OH measurements from baseline to the 1-year follow-up. The corresponding values for those without two OH measurements were 15.5 (IQR: 8.0–20.0) and 13.0 (IQR: 10.0–15.5). There were no significant differences between those with and those without OH regarding MMSE scores (fig. 3) or CDR-SB scores (fig. 4) at baseline or at any of the follow-up examinations (all t test p values ≥0.093).

In total, we had 349 observations of MMSE scores and 350 observations of CDR-SB scores for the 86 patients who were classified as either OH+ or OH–. So-called spaghetti plots of these observations, with LOESS curves fitted to each group separately, are shown in

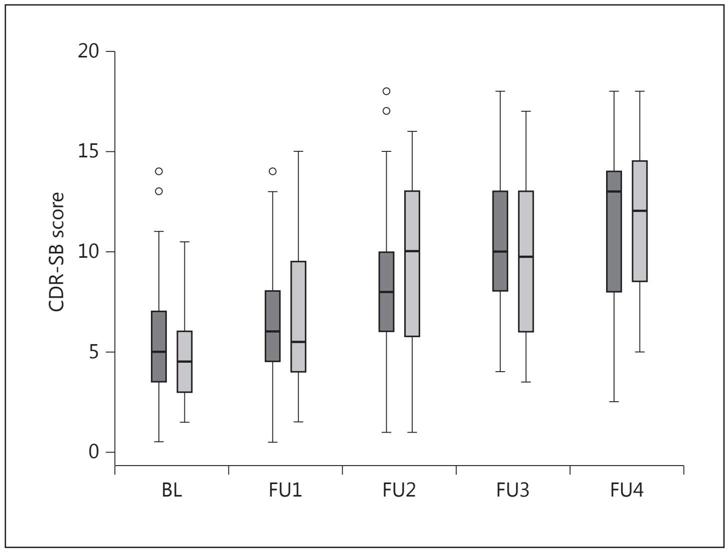

Fig. 4. Box plot of CDR-SB scores from baseline (BL) to 4-year follow-up (FU4). Light grey: patients with OH at each examination. Dark grey: patients without OH at each examination.

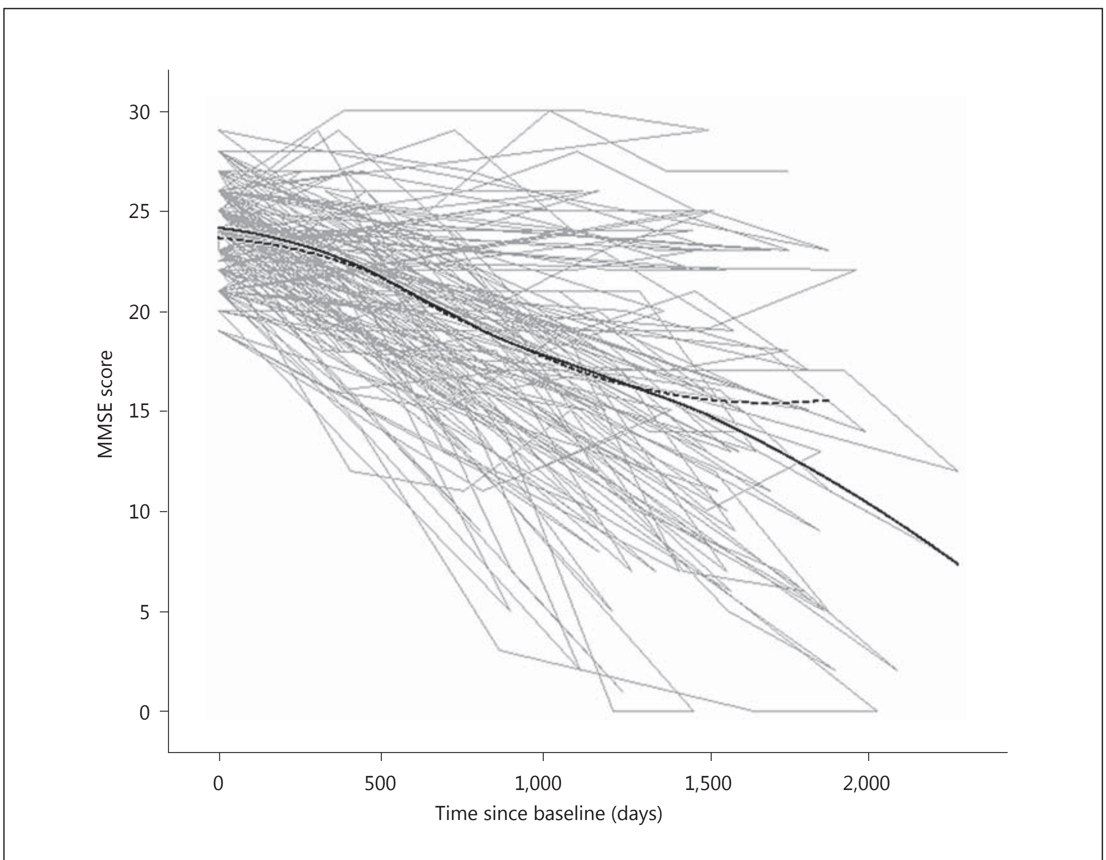

Fig. 5. Course of MMSE scores for 86 patients having either persistent OH (OH+) or never OH (OH–) at baseline and the 1-year follow-up. Observed individual curves (light grey) as well as fitted LOESS curves for the mean responses for the OH– group (solid black line) and for the OH+ group (dashed black line).

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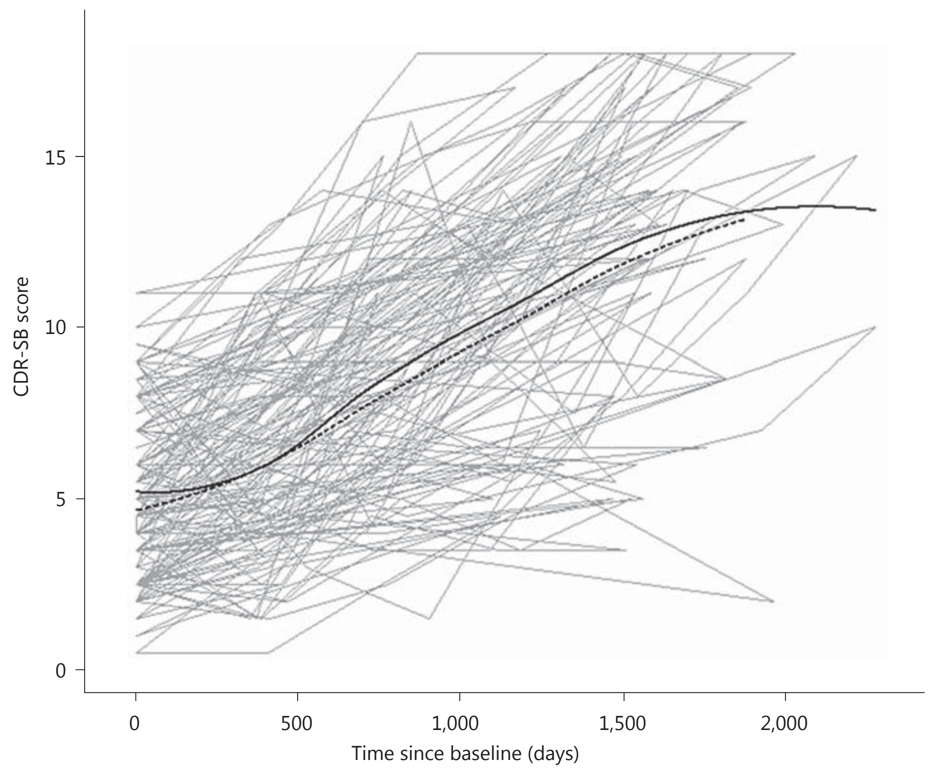

Fig. 6. Course of CDR-SB scores for 86 patients having either persistent OH (OH+) or never OH (OH–) at baseline and the 1-year follow-up. Observed individual curves (light grey) as well as fitted LOESS curves for the mean responses for the OH– group (solid black line) and for the OH+ group (dashed black line).

figures 5 and 6, respectively. These plots seem to imply that OH status has little impact on the course of CDR-SB and MMSE scores, as the LOESS curves are very similar for the OH– and the OH+ groups. The differences are found mostly towards the end, where the data are increasingly scarce. Using GEE modelling (table 3), we found that there was indeed no evidence of a differential longitudinal development in CDR-SB scores according to OH status ($p > 0.76$ for the interaction effect in all models); furthermore, there was no evidence of a difference in scores at baseline ($p > 0.42$). With regard to MMSE scores (table 4), some differences at baseline showed up in the adjusted estimates (models 3 and 4, $p < 0.005$); however, we found little evidence of a difference in the slopes of the curves (all $p \geq 0.24$).

Using the package joineR, we fitted joint models in which the longitudinal and the survival outcomes were linked through common random effects. For CDR-SB scores (table 3), the results from joint modelling were similar to the GEE results, with very small and solidly non-significant interaction effects (OH+/time) and with estimated baseline differences always smaller than 0.5 (in favour of the OH+ group; not statistically significant, $p \geq 0.35$). For MMSE scores (table 4), the evidence of a differential longitudinal development increased somewhat (p values from 0.17 to 0.22); however, the statistically significant differences at baseline disappeared (though still indicated with the lowest p value of 0.063).

Table 3. GEE and joint models for the longitudinal course of CDR-SB scores

	Persistent OH		Time		Interaction	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
GEE						
Model 1[a]	−0.36 (−1.23 to 0.52)	0.423	1.70 (1.46–1.95)	<0.001	0.07 (−0.36 to 0.49)	0.762
Model 2[b]	−0.36 (−1.26 to 0.55)	0.442	1.71 (1.46–1.96)	<0.001	0.05 (−0.37 to 0.47)	0.817
Model 3[c]	−0.46 (−1.79 to 0.88)	0.505	1.71 (1.45–1.97)	<0.001	0.05 (−0.38 to 0.48)	0.830
Model 4[d]	−0.40 (−1.67 to 0.87)	0.535	1.72 (1.46–1.98)	<0.001	−0.01 (−0.43 to 0.41)	0.956
Joint						
Model 1[a]	−0.43 (−1.60 to 0.59)	0.361	1.75 (1.42–2.04)	<0.001	0.06 (−0.43 to 0.64)	0.670
Model 2[b]	−0.43 (−1.48 to 0.55)	0.350	1.75 (1.46–2.03)	<0.001	0.06 (−0.40 to 0.53)	0.778
Model 3[c]	−0.27 (−2.36 to 1.52)	0.656	1.82 (1.48–2.14)	<0.001	0.01 (−0.45 to 0.53)	0.870
Model 4[d]	−0.35 (−1.97 to 1.14)	0.605	1.84 (1.48–2.16)	<0.001	−0.04 (−0.53 to 0.53)	0.989

[a] 'Unadjusted' (n = 86). [b] Adjusted for age and sex (n = 86). [c] Adjusted for all candidate covariates (n = 78). [d] Adjusted for age, sex, centre, smoking, antidementia medication, cardiovascular disease, education, and MMSE score at baseline (n = 79).

Table 4. GEE and joint models for the longitudinal course of MMSE scores

	Persistent OH		Time		Interaction	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
GEE						
Model 1[a]	−0.49 (−1.38 to 0.39)	0.274	−2.41 (−2.87 to −1.96)	<0.001	0.36 (−0.45 to 1.17)	0.383
Model 2[b]	−0.56 (−1.52 to 0.40)	0.254	−2.41 (−2.85 to −1.96)	<0.001	0.37 (−0.44 to 1.17)	0.370
Model 3[c]	−2.08 (−3.47 to −0.68)	0.004	−2.57 (−3.02 to −2.12)	<0.001	0.46 (−0.31 to 1.22)	0.240
Model 4[d]	−1.89 (−3.08 to −0.69)	0.002	−2.45 (−2.86 to −2.02)	<0.001	0.34 (−0.41 to 1.09)	0.377
Joint						
Model 1[a]	−0.69 (−1.77 to 0.34)	0.181	−2.72 (−3.25 to −2.15)	<0.001	0.55 (−0.36 to 1.46)	0.214
Model 2[b]	−0.58 (−1.75 to 0.58)	0.313	−2.68 (−3.13 to −2.22)	<0.001	0.53 (−0.35 to 1.45)	0.223
Model 3[c]	−1.08 (−2.27 to 0.13)	0.063	−2.81 (−3.40 to −2.18)	<0.001	0.72 (−0.28 to 1.67)	0.172
Model 4[d]	−0.70 (−1.71 to 0.22)	0.117	−2.74 (−3.25 to −2.16)	<0.001	0.60 (−0.38 to 1.58)	0.219

[a] 'Unadjusted' (n = 86). [b] Adjusted for age and sex (n = 86). [c] Adjusted for all candidate covariates (n = 76). [d] Adjusted for age, sex, centre, CDR-SB score (at baseline), and CIRS score (n = 82).

Discussion

This is one of a few studies exploring the longitudinal course and clinical predictive power of OH in older individuals with dementia. The point prevalence of OH was 44% at baseline and remained in the range of 30–45% during the study period. The persistence of OH from one year to the next was around 50%, although only about 10% of the patients had OH at 3 successive examinations. One might perhaps expect an increasing OH prevalence over time due to ageing and associated baroreflex impairments [4, 50]. Such an increase was not observed, however. This could be due to individuals with OH having a higher mortality rate [17], thus keeping the prevalence relatively constant, or due to the moderate length of our follow-up period. An alternative explanation is, as indeed our findings suggest, that the prevalence of OH in dementia is rather constant, even as the dementing disease progresses. It is possible that OH is caused by changes occurring early in the disease course. However, this might differ between various types of dementia. Due to the incompleteness of the relevant data, and also the relatively few patients in the non-AD groups, we were not able to fully explore this question. The rather constant prevalence of OH conceivably also could be due to adjustments of medications potentially contributing to OH, in response to a diagnosis of OH, or for other reasons. The lack of relevant data precluded adjusting for this potential contributing factor. Dehydration, which may be a prevalent problem in nursing home residents [51], might possibly also have affected the observed prevalence of OH, as more of the patients became nursing home residents due to progression of their dementia. Nevertheless, no increase in OH prevalence was observed.

In two cross-sectional studies including patients with mild and moderate dementia, point prevalence values similar to ours were found for OH [6, 9] in the AD and VaD groups, but higher values in the LBD group, which also appeared to have a more prolonged period of OH. These studies employed a longer standing OH measurement period with more measurement points [52] and more precise measurement devices than our study.

Regarding the longitudinal functional implications of OH, our results, which are in line with those of a previous study [15], did not confirm the hypothesis that having persistent OH predicts a more rapid cognitive and functional decline in these patients, at least not with regard to function as measured with the CDR-SB. However, with respect to cognitive function as measured with the MMSE, there seems to be some weak evidence of an association with OH status. Notably, both MMSE scores and CDR-SB scores are rather unspecific outcome measures, and the employment of more specific and sensitive instruments might have produced different results. Still, with respect to the MMSE, a study of cognitive functions in patients with neurogenic OH found OH to be associated with impairment of global cognitive functioning as well as more specific tasks, mainly concerning executive functions [53]. Furthermore, both of these instruments have been used to follow the course of AD, DLB, and VaD in previous studies [54–56]. Although the neuropsychological profiles of AD and DLB are different [57], the longitudinal decline in MMSE scores has been shown to be equivalent [55].

The course towards the end of the follow-up period of both the MMSE and the CDR-SB scores raises suspicion with regard to a 'healthy survivor' effect, which might possibly influence the results in the 'persistent' OH and the 'never' OH groups differently. An approach to account for biases because of informative dropout due to death is to model the longitudinal and the survival responses jointly [45–47]. Even though there do not seem to be any substantial differences in mortality rates between the two groups, there may be differences as to *who* died. In the joint models, we found significant link parameters, implying that there were latent associations between the longitudinal and the survival processes. Even so, these extended analyses did not change our conclusions.

In contrast to a previous study including patients with LBD only [17], we found no association between persistent OH and survival. Notably, our study differs from this study with respect to both the types of dementia involved and the definition of persistent OH.

Our study has some limitations. These include the relative lack of standardisation of the OH measurements, with only 1 standing OH measurement in most cases within a period limited to 3 min, a sizeable proportion of OH measurements starting from the sitting instead of the supine position, and the lack of a predetermined preceding period of rest. Furthermore, manual sphygmomanometers were employed instead of more precise devices, and the clinicians performing the measurements did not receive any particular training in OH measurement prior to the study. These factors may have led to an underestimation of the prevalence of OH [52, 58].

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A proportion of the patients had missing data at some assessments, which may have resulted in less precise estimates of OH prevalence. However, except for data missing due to death, these missing data were random, and thus there was probably no systematic selection bias, suggesting that these factors did not systematically influence the findings. Still, our results should be interpreted with some caution.

We realise that the study may not have the statistical power needed for us to discover potential small prognostic correlates of OH, and that some of the models used may have been over-parameterised considering the sample size. The confidence intervals for the effects of OH on MMSE and CDR-SB scores are all quite wide, reflecting the limited amount of data on a subject of substantial complexity. For the MMSE, plausible values for yearly change for the OH+ group versus the OH– group range from about –0.4 to +1.5; for the CDR-SB, every value between –0.5 and +0.5 is plausible. The point estimates, however, were relatively consistent in all the models and point towards no clinically relevant effect of having persistent OH either on survival or on the baseline level or longitudinal course of CDR-SB scores. As stated above, with regard to the longitudinal course of MMSE scores, there seems to be some weak evidence of an association with OH status, but this clearly should be explored in a larger sample.

The strengths of this study include its prospective design, the relatively large sample of participants recruited from various centres, the inclusion of all common dementia subtypes, its comprehensive evaluation programme, the availability of data on a number of established or potential prognostic factors, and the comparatively long follow-up period.

In conclusion, OH was moderately prevalent and persistent over time in a sample of older individuals initially having mild dementia. Our results did not confirm the hypothesis that persistent OH would predict a more rapid cognitive and functional decline in these patients or shorter survival. However, being a rather common and potentially treatable condition, and due to its association with falls, OH should be actively looked for in patients with dementia. Future studies should include a larger sample and use more rigorous methods for OH measurement.

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